

	Title 43USC1633 Protocol	Doc id MA-33723
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Effective date: 2017-04-10 14:21

A Multicenter, Open-Label, Prospective Study of Cannula Injection of *Restylane® Lyft with Lidocaine* for Cheek Augmentation and the Correction of Age Related Midface Contour Deficiencies

Study products: *Restylane® Lyft with Lidocaine*

Clinical trial number (CTN): 43USC1633

Sponsor: Q-Med AB, a Galderma affiliate



Confidentiality Statement

This study protocol contains confidential information belonging to Q-Med AB, a Galderma affiliate. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and neither disclose it to any third parties (except where required by applicable law) nor use it for any other purpose than in relation to the clinical study described herein.

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Summary of Changes in Clinical Study Protocol from Version 1.0 to Version 2.0

The changes, including rationale, are described in the table below.

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]

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Sponsor:

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Medical expert:

Clinical Project Manager:

Study Statistician:

Medical expert:

Clinical Project Manager:

Study Statistician:

Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a clinical investigational plan (CIP) amendment.

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Sponsor Signatures

The CIP is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.

Medical Expert, Q-Med AB,

[REDACTED]

Head of Global A&C Clinical Development, Q-Med AB

[REDACTED]

Clinical Project Manager, Galderma R&D, LLC

[REDACTED]

Statistician, Q-Med AB

[REDACTED]

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Signed Agreement of the Clinical Study Protocol

CTN: 43USC1633

Title of the CIP: A Multicenter, Open-Label, Prospective Study of Cannula Injection of *Restylane® Lyft with Lidocaine* for Cheek Augmentation and the Correction of Age Related Midface Contour Deficiencies

I, the undersigned, have read and understand the CIP specified above, and agree on the contents. The CIP, the clinical trial agreement (CTA) and the additional information given in the IFU and Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name

Signature

Date

Study site name and address


Study site number

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Synopsis

Title of study:	A Multicenter, Open-Label, Prospective Study of Cannula Injection of <i>Restylane® Lyft with Lidocaine</i> for Cheek Augmentation and the Correction of Age Related Midface Contour Deficiencies
Clinical Trial Number:	43USC1633
Countries involved	United States
Number of sites	Approximately 6
Number of Subjects	Approximately 60 subjects
Target Indication	Cheek Augmentation and the Correction of Age Related Midface Contour Deficiency with use of a cannula (in the range of 23G-27G) in subjects 22 years of age or older.
Primary Safety Objective and Endpoints	<p>The primary objective of the study is to assess the adverse events of <i>Restylane® Lyft with Lidocaine</i> in conjunction with the use of a small blunt tip cannula (in the range of 23G-27G) for cheek augmentation and the correction of age related midface contour deficiency.</p> <ul style="list-style-type: none"> incidence, intensity, and duration of all adverse events (AEs) as collected throughout the study and incidence, intensity and duration of pre-defined, expected, post-treatment events reported during the first 2 weeks after treatment as recorded in the subject diary. safety assessments of midface firmness, symmetry, sensation, mass formation and product palpability as evaluated by designated study staff.
Secondary Effectiveness Objectives and Endpoints	<p>To evaluate the effectiveness of <i>Restylane® Lyft with Lidocaine</i> used in conjunction with a small blunt-tip cannula (in the range of 23G - 27G), for cheek augmentation and the correction of age related midface contour deficiency.</p> <ul style="list-style-type: none"> <div data-bbox="715 1536 1473 2002" style="background-color: black; width: 100%; height: 100%; min-height: 200px;"></div>

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Study Design	Open-label, multi-center, single-arm, US study
Subject Participation	A subject's duration in the study is approximately 5.0 months from screening to final follow-up visit.
Enrollment	<p>Written informed consent will be obtained before any study related procedure is performed. Subjects will be screened for eligibility within 14 days prior to injection. The screening visit and baseline visit may be performed on the same day.</p> 
Treatment	<p><i>Treatment</i></p> <p>The subjects will be treated with <i>Restylane® Lyft with Lidocaine</i> in the right and left sides of the mid-face. Sufficient amount of study product should be injected to achieve optimal correction of the mid-face, in the opinion of the Investigator.</p> <p><i>Re-Treatment</i></p> <p>At the Week 16 visit, the subjects will be offered an optional <i>Restylane® Lyft with Lidocaine</i> treatment if optimal aesthetic improvement is not maintained.</p>
Study Procedures	<p><i>Evaluation of safety</i></p> <p>Adverse Events (AEs) will be obtained from signs and symptoms reported by the subject or detected during each examination visit to obtain information about any medical occurrence that meets the definition of an AE. In addition to the interview, all subjects will complete a Diary for 14 days after treatment at baseline. Diary data will be counted and evaluated separately from AE data. Any other type of symptom recorded in the Diary will be assessed and tabulated verbatim. Any subject with a treatment related AE that is ongoing at the time of study completion will be followed until that AE is resolved or stabilized. Any AE assessed as related to the study product or injection procedure with onset after subject participation in the study is over, and that the Investigator becomes aware of, should be reported to Sponsor.</p> <p><i>Safety Assessments</i></p> <p>Midface firmness, symmetry and function will be performed using scales at screening, baseline and all physical visits thereafter. These parameters will be rated as "Normal" or "Abnormal". All abnormal ratings will be further assessed as mild, moderate, or severe and all test scores will be recorded.</p>

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	<p>Midface sensation will be tested at all physical study visits using two methods:</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Mass formation will be performed at screening/baseline and all physical visits thereafter.</p> <p>Device palpability will be assessed at each scheduled post-treatment visit and will assess whether or not the palpability is the normal expected feel. An unexpected feel is to be recorded as an adverse event.</p> <p><i>Evaluation of effectiveness</i></p> <p>Before initial treatment at the Baseline/Day 1 visit and at each physical follow-up visit, the investigator will perform a live assessment of both the subjects' right and left midface [REDACTED]</p> <p>Aesthetic improvement of each side of the midface will be a live assessment by the subject and the Investigator, independent of each other, at each physical follow-up visit [REDACTED]</p> <p>Subject Satisfaction with outcome will be recorded [REDACTED]</p> <p>Study report</p> <p>A study report will be compiled at the conclusion of the study. This report will be included in the regulatory submission for a marketing application.</p>
Inclusion criteria:	<ol style="list-style-type: none"> Subjects willing to comply with the requirements of the study and providing a signed written informed consent. Males or non-pregnant, non-breastfeeding females, 22 years of age or older. <p>[REDACTED]</p> <ol style="list-style-type: none"> Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures for the duration of the study (e.g., laser or chemical resurfacing, facelift, etc.). Subjects

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	<p>may have facial cosmetic procedures outside the area of assessment (e.g., neurotoxin injections above the orbital rim, etc.) either before or contemporaneously with cheek augmentation and correction of age related midface contour deficiency.</p> <p>5. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the screening/enrollment visit, prior to treatment/injection, and at the exit visit.</p> <p>Acceptable forms of effective birth control include:</p> <ul style="list-style-type: none"> • Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository; • Bilateral tubal ligation; • Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1; • Hormonal intra uterine device (IUD) inserted at least 28 days prior to Day 1; • Vasectomised partner (in monogamous relationship) for at least 3 months prior to screening; • Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study) <p>6. Passed functionality and sensory tests.</p> <p>7. Negative urinary pregnancy test for women of childbearing potential at the screening and injection visit.</p>
Exclusion criteria:	<ol style="list-style-type: none"> 1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid gel or to gram positive bacterial proteins. 2. History of allergy or hypersensitivity to lidocaine or other amide-type anaesthetics, or topical anaesthetics or nerve blocking agents (if such products are intended to be used for that subject). 3. History of severe or multiple allergies e.g., manifested by anaphylaxis. 4. History of or active collagen diseases or autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, skin or systemic sclerosis. 5. History of radiation of or presence of cancerous or precancerous lesions (e.g., actinic keratosis) or tattoo in the treatment area. 6. History of bleeding disorders or use of concomitant medication that has the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation

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	<p>(e.g. aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs}, omega 3 or vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.</p> <ol style="list-style-type: none"> 7. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies), systemic corticosteroids (inhaled corticosteroids are allowed) within 3 months before study treatment. 8. Treatment with systemic retinoids within 6 months, topical (facial) prescription retinoids or corticosteroids below the level of the lower orbital rim within 1 month before study treatment. 9. Have undergone prior surgery to midface including facial plastic surgery, lifting threads, tissue grafting, or tissue augmentation with permanent implants, silicone, fat, or other permanent or semi-permanent dermal fillers, or is planning to undergo any of these procedures affecting the treatment area, at any time during the study. 10. History of other facial treatment/procedure in the previous 6months below the level of the lower orbital rim that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g., dental work, dental root or sinus surgery, or resurfacing (laser, photomodulation, intense pulsed light [IPL], radio frequency, dermabrasion, chemical peel or other ablative/non-ablative procedures), or mesotherapy, or neurotoxin injections, or is planning to undergo any of these procedures affecting the treatment area, at any time during the study. 11. Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months prior to any study injections. 12. Have received any other therapy, which, in the opinion of the investigator, could interfere with safety or efficacy evaluations. 13. History of or the presence of any disease, in the area to be treated which may result in changes in facial contour or edema of the face during the course of the study, such as inflammation, active or chronic infection (e.g. in mouth, dentals, sinuses etc.), facial psoriasis eczema, acne, rosacea, perioral dermatitis, herpes zoster, acanthosis, etc. 14. Have a history of prior significant trauma resulting in scarring, fibrosis or deformation in the area to be treated.
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	<p>[REDACTED]</p> <ol style="list-style-type: none"> 16. A dental or oral status on visual inspection that, in the Treating Investigator's opinion makes the subject unsuitable for inclusion. 17. The presence of moderate or severe abnormal rating for firmness or detection of any abnormal midfacial structure, such as a scar or lump. 18. The presence of moderate or severe abnormal rating for midface symmetry. 19. The presence of abnormal rating in midface function, with inability to effectively puff cheeks, smile broadly, or chew. <p>[REDACTED]</p> <ol style="list-style-type: none"> 21. Subjects participating in another interventional clinical study within 30 days of screening. 22. Intention to lose a significant amount of weight during the study period. 23. Any medical condition that, in the opinion of the Treating Investigator, would make the subject unsuitable for inclusion. 24. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g., subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result. 25. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
Investigational product:	<p><i>Restylane Lyft with Lidocaine</i> 1 mL injectable gel containing 0.3% lidocaine is supplied sterile in a 1 mL prefilled glass syringe with a luer-lock fitting packaged in a blister.</p> <p><i>Restylane Lyft with Lidocaine</i> is to be injected with a cannula in the range of 23G-27G (inclusive), into the midface at the supraperiosteal to subcutaneous layer inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides.</p> <p>The specific brand of cannula used for injection is up to the discretion of the Treating Investigator, provided the cannula is cleared for use in the US and that the cannula bore is 23G-27G</p>

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	<p>(inclusive). Cannula length depends on the injection technique and the anatomic location being treated; in general, cannula length ranging from 1 - 2 inches long is recommended. The Treating Investigator should use the amount of dermal filler necessary to achieve an optimal augmentation for each subject, however, it is recommended that a volume not to exceed 6 mL of filler be injected. Optimal augmentation is defined as the best possible aesthetic result that can be obtained for an individual study subject, as agreed upon by the Treating Investigator and subject.</p> <p>The injection technique, including use of anesthesia, is left to the discretion of the Treating Investigator.</p>
Reference therapy	N/A
Schedule of Events	<ul style="list-style-type: none"> • Screening (Day -14 to Day 1). • Treatment visit (Baseline; Day 1). Screening visit and baseline visit can be combined if no washout is needed • Follow-up (telephone contact) 72 hrs • Follow-up after treatment at 2, 4, 8 and 16 weeks <p>For subjects receiving re-treatment at the Week 16 visit:</p> <ul style="list-style-type: none"> • Follow-up (telephone contact) 72 hrs • Follow-up after treatment at 2 weeks
Efficacy Assessment:	<div style="background-color: black; height: 15px; width: 100%;"></div> <div style="background-color: black; height: 15px; width: 100%;"></div> <div style="background-color: black; height: 15px; width: 100%;"></div> <div style="background-color: black; height: 15px; width: 100%;"></div>
Safety Assessment:	<ol style="list-style-type: none"> 1. Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the subject or detected during each examination. 2. A subject diary will be dispensed to all subjects for daily completion over the first 2 weeks after treatment to record the presence of adverse reactions. Information from the diary will be presented separately from AEs. 3. Safety evaluations according to pre-defined methods, at baseline and at each physical follow-up visit.
Statistical Methods:	<p><u>Sample size</u></p> <p>Sixty (60) subjects will be enrolled with the goal of 50 subjects completing the study. The sample size has been established based on the probability of detecting an AE given the true population rate of 5%. This 5% criterion has been selected based on this value representing the point-estimate cut-off AE rate for inclusion in</p>

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	<p>product labelling.</p> <div data-bbox="571 313 1473 506"></div> <div data-bbox="571 512 1473 705"></div> <div data-bbox="571 712 916 757"></div> <div data-bbox="571 763 1147 808"></div> <div data-bbox="571 815 1473 972"></div> <div data-bbox="571 978 1171 1023"></div> <div data-bbox="571 1030 1473 1263"></div> <div data-bbox="571 1270 1473 1350"></div> <div data-bbox="571 1357 1473 1476"></div> <div data-bbox="571 1482 1473 1565"></div>
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Abbreviations and Definitions of Terms

AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
CE	“Conformité Européenne” – the quality and branding mark for products made or sold within the European Union.
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
Childbearing Potential	A female (including pre-menopausal subjects) capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single, women whose husbands have been vasectomised or whose husbands have received or utilizing mechanical contraceptive devices.
CRF	Case report form
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labelling)
DMC	Data monitoring committee
DMP	Data management plan
eCRF	Electronic case report form
ET	Early termination
FDA	United States Food and Drug Administration
First subject in	First subject screened, i.e. who signs the informed consent form
First subject out	First subject who completed their last study visit
G	Gauge
	
GCP	Good clinical practice
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IFU	Instructions for use

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Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intention-to-treat
Last subject in	Last subject who entered the study
Last subject out	Last subject who completed their last study visit
MedDRA	Medical dictionary for regulatory activities
	
NSAID	Non-steroidal anti-inflammatory drugs
PI	Principal Investigator; qualified person responsible for conducting the study at a study site
PP	Per protocol
PT	Preferred term
QA	Quality assurance
RA	Regulatory authority
ROPI	Report of Prior Investigations, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SOC	System Organ Class
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor.
Study files	The Investigator file and the Sponsor file
Study products	The investigational product and the reference product under study
Study site	Institution or site where the study is carried out
TC	Telephone Call

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Tx Treatment
WHO World Health Organization

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1. Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical investigational plan (CIP), good clinical practice (GCP), and applicable regional or national regulations. The international standard for clinical study of medical devices for human subjects, ISO14155:2011 shall be followed. The International Conference on Harmonization (ICH) guideline for GCP (E6) shall be followed as applicable for medical device. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki <http://www.wma.net/en/30publications/10policies/b3/>.

1.2 Application to independent ethics committee and/or regulatory authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CIP/CIP amendment(s) from the independent ethics committee (IEC). The study shall not begin until the required favourable opinion from the IEC has been obtained. The PI shall file all correspondence with the IEC in the Investigator file and copies of IEC approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IEC or regulatory authorities (RA) shall be followed.

The study requires application for approval from the US Food and Drug Administration (FDA). The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

2. Background Information

2.1 Indication and population description

[REDACTED]

[REDACTED]

2.2 Investigational product description

[REDACTED]

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[REDACTED]

[REDACTED]

2.3 Reference product description

Not applicable since this is a single arm study.

2.4 Previous experience

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.5 Study rationale

[REDACTED]

[REDACTED]

2.6 Justification for the design of the study

This clinical study is being conducted to assess the safety of use of *Restylane® Lyft with Lidocaine* in conjunction with a small blunt-tip cannula (in the range of 23G to 27G; cleared for use in US) for cheek augmentation and the correction of age related midface contour deficiencies in subjects over the age of 21.

This is an open-label study, sixty (60) subjects will be enrolled with the goal of 50 subjects completing the study. The sample size has been established based on the probability of detecting an adverse event given the true population rate of 5%.

2.7 Risks and benefits

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ 10. ☐ 11. ☐ 12. ☐ 13. ☐ 14. ☐ 15. ☐ 16. ☐ 17. ☐ 18. ☐ 19. ☐ 20. ☐ 21. ☐ 22. ☐ 23. ☐ 24. ☐ 25. ☐ 26. ☐ 27. ☐ 28. ☐ 29. ☐ 30. ☐ 31. ☐ 32. ☐ 33. ☐ 34. ☐ 35. ☐ 36. ☐ 37. ☐ 38. ☐ 39. ☐ 40. ☐ 41. ☐ 42. ☐ 43. ☐ 44. ☐ 45. ☐ 46. ☐ 47. ☐ 48. ☐ 49. ☐ 50. ☐ 51. ☐ 52. ☐ 53. ☐ 54. ☐ 55. ☐ 56. ☐ 57. ☐ 58. ☐ 59. ☐ 60. ☐ 61. ☐ 62. ☐ 63. ☐ 64. ☐ 65. ☐ 66. ☐ 67. ☐ 68. ☐ 69. ☐ 70. ☐ 71. ☐ 72. ☐ 73. ☐ 74. ☐ 75. ☐ 76. ☐ 77. ☐ 78. ☐ 79. ☐ 80. ☐ 81. ☐ 82. ☐ 83. ☐ 84. ☐ 85. ☐ 86. ☐ 87. ☐ 88. ☐ 89. ☐ 90. ☐ 91. ☐ 92. ☐ 93. ☐ 94. ☐ 95. ☐ 96. ☐ 97. ☐ 98. ☐ 99. ☐ 100. ☐

3.1 Objectives and endpoints

3.1.1 Primary safety objective and endpoint

- incidence, intensity, and duration of all adverse events (AEs) as collected throughout the study and incidence, intensity and duration of pre-defined, expected, post-treatment events reported during the first 2 weeks after treatment as recorded in the subject diary.
- safety assessments of midface firmness, symmetry, sensation, mass formation and product palpability as evaluated by designated study staff.

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3.1.2 Secondary objectives and endpoints

[REDACTED]

- [REDACTED]
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- [REDACTED]
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4. Design of the Study

4.1 General outline

This is a multicenter, open-label, 16-week prospective study of *Restylane® Lyft with Lidocaine* in conjunction with the use of a small blunt tip cannula (in the range of 23G-27G) for cheek augmentation and the correction of age related midface contour deficiency.

[REDACTED]

Subjects' midface will be treated to optimal augmentation. Optimal augmentation is defined as the best possible aesthetic result that can be obtained for an individual study subject, as agreed upon by the treating investigator and subject. It is recommended that a volume not to exceed 6 mL of filler be injected. Cannula length depends on the injection technique; in general, cannula length ranging from 1 to 2 inches long is recommended.

After treatment on Day1, a 72 hour phone call and follow-up visits at 2, 4, 8 and 16 weeks are scheduled.

At the 16-week visit after all study procedures for the visit are completed, subjects can receive an optional additional treatment if optimal aesthetic improvement is not maintained.

A Schedule of Events is provided below in 4.7.

4.2 Number of subjects

Subjects will be recruited from up to 6 study sites in the USA. Approximately 60 subjects will be included in the study.

4.3 Duration of subject participation

A subject may be involved in the study for approximately 5.0 months from screening to the final follow-up visit. "End of study" is defined as the time point when the last subject has completed the last study visit.

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If a treated subject has used any of the above prohibited medications or procedures he or she should, for safety reasons, continue in the study for the scheduled follow-up visits.

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4.8 Visits

- [REDACTED]
- [REDACTED]
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- [REDACTED]

[REDACTED]

■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
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Gender	Percentage
Male	35%
Female	45%
Other	10%
Unknown	10%

Response	Percentage
U.S. should take action	71%
U.S. should not take action	27%
U.S. should take action, but only if other countries do first	2%

5.1 Subject information and informed consent

The Investigator or his/her authorized designee must always use the IRB-approved subject information and informed consent form and it must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

It is the responsibility of the Investigator or his/her authorized designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study, e.g. explain the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB. The subject shall be informed that the participation is confidential and voluntary and that the subject has the right to withdraw from the study at any time, without any effect on his/her future medical care, treatment or benefits to which the subject is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the informed consent form and to consider participation in the study. Before any study-related activities are performed, the informed consent form shall be personally signed and dated by the subject and the Investigator or his/her authorized designee responsible for conducting the informed consent process.

All original signed informed consent forms shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated informed consent form and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study.

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5.2 Inclusion criteria

The subjects must meet the following criteria to be eligible for the study:

1. Subjects willing to comply with the requirements of the study and providing a signed written informed consent.
2. Males or non-pregnant, non-breastfeeding females, 22 years of age or older.

3. [REDACTED]
4. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures for the duration of the study (e.g., laser or chemical resurfacing, facelift, etc.). Subjects may have facial cosmetic procedures outside the area of assessment (e.g., neurotoxin injections above the orbital rim, etc.) either before or contemporaneously with cheek augmentation and correction of age related midface contour deficiency.
5. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test at the screening/enrollment visit, prior to treatment/injection, and at the exit visit.

Acceptable forms of effective birth control include:

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository;
 - Bilateral tubal ligation;
 - Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1;
 - Hormonal intra uterine device (IUD) inserted at least 28 days prior to Day 1;
 - Vasectomised partner (in monogamous relationship) for at least 3 months prior to screening;
 - Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study)
6. Passed functionality and sensory tests.
 7. Negative urinary pregnancy test for women of childbearing potential at the screening and injection visit.

5.3 Exclusion criteria

The presence of any of the following exclusion criteria will exclude a subject from enrolment in the study:

1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid gel or to gram positive bacterial proteins.
2. History of allergy or hypersensitivity to lidocaine or other amide-type anaesthetics, or topical anaesthetics or nerve blocking agents (if such products are intended to be used for that subject).


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3. History of severe or multiple allergies e.g., manifested by anaphylaxis.
4. History of or active collagen diseases or autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, skin or systemic sclerosis.
5. History of radiation of or presence of cancerous or precancerous lesions (e.g., actinic keratosis) or tattoo in the treatment area.
6. History of bleeding disorders or use of concomitant medication that has the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g. aspirin or other non-steroidal anti-inflammatory drugs [NSAIDs}, omega 3 or vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
7. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., monoclonal antibodies), systemic corticosteroids (inhaled corticosteroids are allowed) within 3 months before study treatment.
8. Treatment with systemic retinoids within 6 months, topical (facial) prescription retinoids or corticosteroids below the level of the lower orbital rim within 1 month before study treatment.
9. Have undergone prior surgery to midface including facial plastic surgery, lifting threads, tissue grafting, or tissue augmentation with permanent implants, silicone, fat, or other permanent or semi-permanent dermal fillers, or is planning to undergo any of these procedures affecting the treatment area, at any time during the study.
10. History of other facial treatment/procedure in the previous 6months below the level of the lower orbital rim that, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessments or exposes the subject to undue risk by study participation, e.g., dental work, dental root or sinus surgery, or resurfacing (laser, photomodulation, intense pulsed light [IPL], radio frequency, dermabrasion, chemical peel or other ablative/non-ablative procedures), or mesotherapy, or neurotoxin injections, or is planning to undergo any of these procedures affecting the treatment area, at any time during the study.
11. Previous use of any HA based or collagen based biodegradable facial tissue augmentation therapy below the level of the lower orbital rim within 12 months prior to any study injections.
12. Have received any other therapy, which, in the opinion of the investigator, could interfere with safety or efficacy evaluations.
13. History of or the presence of any disease, in the area to be treated which may result in changes in facial contour or edema of the face during the course of the study, such as inflammation, active or chronic infection (e.g. in mouth, dentals, sinuses etc.), facial psoriasis eczema, acne, rosacea, perioral dermatitis, herpes zoster, acanthosis, etc.
14. Have a history of prior significant trauma resulting in scarring, fibrosis or deformation in the area to be treated.



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16. A dental or oral status on visual inspection that, in the Treating Investigator's opinion makes the subject unsuitable for inclusion.
17. The presence of moderate or severe abnormal rating for firmness or detection of any abnormal midfacial structure, such as a scar or lump.
18. The presence of moderate or severe abnormal rating for midface symmetry.
19. The presence of abnormal rating in midface function, with inability to effectively puff cheeks, smile broadly, or chew.

- 
21. Subjects participating in another interventional clinical study within 30 days of screening.
 22. Intention to lose a significant amount of weight during the study period.
 23. Any medical condition that, in the opinion of the Treating Investigator, would make the subject unsuitable for inclusion.
 24. Other condition preventing the subject from entering the study in the Treating Investigator's opinion, e.g., subjects not likely to avoid other facial cosmetic treatments, subjects anticipated to be unreliable, unavailable or incapable of understanding the study assessments or having unrealistic expectations of the treatment result.
 25. Study site personnel, close relatives of the study site personnel (e.g., parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.

5.4 Screening and subject numbers

Prior to any study procedures being conducted, the subject must sign the informed consent form. The subject number will be assigned at Baseline / Day 1. All study procedures performed should be documented in the subject's source documents and in the eCRFs. The subject number, subject name and other information sufficient to link the eCRF to the medical records (e.g. national identification number, chart number, etc.) should be recorded.

A screen failure is a subject who signed informed consent but never enrolled (i.e. received treatment) in the study. For screen failures, the subject's source documents should indicate which assessments have been made and the reason why the subject was discontinued.

A subject is considered enrolled when they have signed the informed consent and are injected at Day 1.

5.5 Withdrawal of subjects

Each subject shall be advised in the informed consent form that the subject has the right to withdraw from the study at any time, for any reason, without prejudice. Subjects may also be discontinued from this study if the Investigator determines that it is in the subject's best interest to do so, and may be withdrawn at the Investigator's discretion at any time.

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The reason and date for withdrawal should be documented in the subject's source documents and eCRFs. When possible, an explanatory comment should be added to further explain the reason for withdrawal. If withdrawal of a subject occurs during a regular investigational visit, the eCRF for that specific visit should be completed as far as possible.

If withdrawal of a subject occurs between regular study visits the subject should, when possible (irrespective of the reason for withdrawal) be scheduled for a termination visit to document subject outcome for the primary and secondary endpoints.

If a subject is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses.

Subjects who receive product and are withdrawn or discontinued from the study will not be replaced.

For AEs still ongoing at the time of the withdrawal, see (Section 8.5.6).

6. Study Products

6.1 Investigational product

The investigational device (i.e. the study product) is *Restylane Lyft® with Lidocaine* manufactured by Q-Med AB, a Galderma affiliate located in Uppsala, Sweden. [REDACTED]

Detailed product information is provided in the instructions for use (IFU).

6.2 Additional products and material

Galderma will provide pregnancy tests.

Topical or local anaesthesia/nerve block may be used at the discretion of the treating Investigator before the treatment. If used, the anaesthesia shall be supplied by the study site. Type of anaesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

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Small blunt tip cannulas within the range of 23 -27 Gauge [G] will be supplied by the study site

6.3 Packaging, labelling, and storage

6.3.1 Investigational product

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.3.2 Reference product

Not applicable.

6.4 Product accountability

The study products will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB and the CTA has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location, with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

When the study is completed, all unused or expired study product at each study site shall be returned to the Sponsor representative for destruction, or be destroyed locally at the site if documented as agreed with Sponsor.

Any malfunctioning study products shall be reported as described in Section 8.6.

Products deliberately or accidentally destroyed during shipment or at a study site shall be accounted for and documented. Used syringes, needles, and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the site. Disposal of hazardous material, i.e. syringes and needles must conform to applicable laws and regulations. The study products must not be used outside the study.

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6.5 Treatment

[REDACTED] **[REDACTED]**

[REDACTED]

[REDACTED]

[REDACTED]

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6.5.6 Treatment compliance

Not applicable; the treatment will be administered by the injector at the investigational site.

7. Efficacy Assessments

7.1 General information

The methods for collecting efficacy data are described in the following sections. To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

7.2 Photography

Photographs will be taken prior to the injection of the study product at the screening/baseline visit. The photographs may be used as a reference in the GAIS assessment. Note that no covering make-up should be used during the photographing session. Personnel will be thoroughly trained in the photographic equipment and techniques before the study start. If the photographs are considered to be of good quality the investigator may proceed with treatment of the subject at the Baseline/ Day 1 visit and if not, a new photograph will be taken prior to treatment.

The photographs shall be taken in a standardised way according to the provided photograph instructional guide.

Each photograph will be identified by the study number, subject number and the visit date at which the photograph was taken. In order to maintain confidentiality, the photographs must not include any information that may reveal the subject's identity.

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[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
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8. Safety Assessments

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[REDACTED]

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AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.4 Laboratory assessments

Pregnancy Test

For all women of childbearing potential, a urine pregnancy test will be performed at screening and baseline (prior to treatment) and at study exit. The test result will be documented in the source documents and eCRF.

8.5 Adverse events

8.5.1 Definition of an adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons¹, whether or not related to the study product.

This definition includes:

- events related to the investigational product or the reference product
- events related to the procedures involved

¹ For users or other persons, this definition is restricted to events related to the investigational product.

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8.5.2 Definition of a serious adverse event

A serious adverse event (SAE) is an AE that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 1. a life-threatening² illness or injury, or
 2. a permanent impairment of a body structure or body function, or
 3. in-patient or prolonged hospitalisation³, or
 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to foetal distress, foetal death, or a congenital abnormality or birth defect

An AE does not need to be recorded as a SAE if it only represents a relapse or an expected change or progression of the condition that was the cause of the treatment, without the development of new symptoms and signs.

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as a SAE rather than not report as such (see section 8.5.5).

8.5.3 Recording instructions

Each subject with an AE occurring after signing of the informed consent form through study exit should be fully recorded in the source document for further transcription to the eCRF. Each subject should be questioned about AEs at each study visit following the screening visit. The question asked should be: “Since your last clinical visit have you had any health problems?” Information on AEs can also be obtained from signs and symptoms detected during each examination.

When an AE is related to a device deficiency including technical device malfunction, the AE should be recorded in the AE eCRF and technical complaint should be reported separately on the study complaint form.

Investigators, or other study site personnel, shall record all AEs in the eCRF, including:

- a) Event term (recorded in standard medical terminology and avoiding abbreviations)
- b) Description of event and affected area
- c) Start date (first day with symptoms)
- d) Stop date (last day with symptoms)
- e) Intensity (mild, moderate, or severe according to definition in Section 8.5.3.1)
- f) Seriousness (serious or not serious, according to definition in Section 8.5.3.2)

² The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

³ Planned hospitalisation for a pre-existing condition, or a procedure required by the CSP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

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- g) Causal relationship to study product or study product injection procedure (yes or no)
- h) Action taken (none, medication treatment, non-medication treatment, or other procedures/tests, subject withdrawn)
- i) Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/stable, not recovered at the end of the study)

The pre-defined, expected post-treatment events shall be assessed separately. These events shall be collected by subjects in a diary used daily for 14 days after the treatment.

8.5.3.1 Intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable)

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

8.5.3.2 Causal relationship and seriousness

Each AE, serious as well as non-serious, shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- “Do you consider that there is a reasonable possibility that the event may have been caused by the study product?”, and
- “Do you consider that there is a reasonable possibility that the event may have been caused by the device injection procedure?”

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfil regulatory requirements.

8.5.4 Reporting of adverse events

Adverse event reporting on each subject shall start at screening visit after the signature of the ICF. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious, are to be reported as an AE in the eCRF.

8.5.5 Reporting of serious adverse events

The Investigator shall report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail.

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In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- CTN: 43USC1633
- Subject identification (age, gender, subject number)
- Adverse event description
- Date when AE occurred
- Date when AE became serious
- Name of Investigator and original reporter (if other than the Investigator)
- Name of investigational device: *Restylane[®] Lyft with Lidocaine*
- Treatment specification

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator or designated study staff.

Supporting documentation to be provided with the SAE report:

- Concomitant medication form
- Concomitant procedure/treatment form
- AE form
- Medical history form
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)

E-mail for reporting: [REDACTED]

The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed to the Sponsor. A copy of the fully completed SAE form shall be kept at the site.

In addition, the Investigator shall report SAEs to the responsible IRB without undue delay, if applicable according to national regulations. The Investigator is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

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8.5.6 Follow-up of ongoing related events after termination of the study and events with onset after termination of study (subject last visit)

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, or assessed as chronic or stable. All AEs assessed as related to the study product or treatment procedure, serious as well as non-serious, with onset after the study termination (last subject study visit), and that the Investigator becomes aware of, should be reported to Sponsor in accordance with the post-marketing procedure as agreed upon with the corporate device vigilance group and the safety management plan.

8.5.7 Pregnancy

Pregnancy itself is not regarded as an AE.

If there is a pregnancy after the subject has been treated, the subject must continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period after treatment must be reported by the Investigator on a pregnancy report form immediately upon acknowledgement and submitted to the Sponsor according to contact details specified in section 8.5.5. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to foetal distress, foetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigators awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalisation, shall be reported and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

8.5.8 Anticipated adverse events

Information regarding anticipated AEs is included in the Instructions for Use.

8.6 Device deficiencies

8.6.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety⁴, or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

8.6.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator or qualified designee. The type of complaint shall be described

⁴ Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to section 8.5.5). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

- Suitable action had not been taken,
- Intervention had not been made or,
- Circumstances had been less fortunate

In Part B of the clinical study complaint form the Sponsor will make the same assessment.

8.6.3 Reporting of device deficiencies

The Investigator shall send the completed clinical study complaint form to the Sponsor using the contact details specified in section 8.5.5. A device deficiency that led to a SAE and any device deficiency that could have led to a SAE shall be reported within 24 hours after the Investigator's awareness in accordance to section 8.5.5

In order to fulfil regulatory reporting requirements, all deficiencies with the study product must be assessed by both the Investigator and the Sponsor to determine if it could have led to a SAE.

If a SAE has resulted from a device deficiency or if either the Investigator or the Sponsor assesses that the device deficiency could have led to a SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IEC.

The deficient study product shall be kept by the study site until the QA complaints group has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

9. Data Handling and Management

9.1 Data management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for handling eCRFs, database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens and program will be designed in accordance with the CIP and the eCRF. Data validation will be performed by computerised logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and medical dictionary for regulatory activities (MedDRA) dictionaries as specified in the DMP. SAEs in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

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9.2 Electronic case report forms

A 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An eCRF is required and shall be completed electronically for each screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data shall be entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the Investigator shall complete data collection. Appropriate training and security measures shall be completed with all authorized investigation site personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and shall not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

Any delegation of collection of data shall be specified in a signature and delegation log.

9.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorised designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorised designee. The appropriate study site personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

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9.2.3 User identification

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

9.2.4 Audit trail

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

9.3 Source documents

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These shall be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, shall be clearly identified with the CTN and subject number. Any personal information, including name, shall be removed or rendered illegible to preserve individual confidentiality.

9.4 Record keeping and access to source data

The Investigator/Institution shall permit study-related monitoring, audits, IRB review, and RA inspections and shall provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed informed consent forms and detailed records of study product accountability). The records shall be retained by the Investigator as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records shall be documented and the Sponsor shall be informed in writing.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, informed consent forms, study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures shall be

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taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the Investigator's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

10. Statistical Methods

10.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed.

[REDACTED]

[REDACTED]

10.2 Analysis populations

The following populations will be defined:

- Safety Includes all subjects who were injected at least once.
- Intention-to-treat (ITT) Includes all subjects who were injected at least once and meet the inclusion criteria for MMVS.

Safety population will be the basis for all safety evaluations. When performing effectiveness analysis, the ITT population will be used.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints and subject characteristics will be presented using descriptive statistics as appropriate.

10.4 Efficacy analysis

[REDACTED]

[REDACTED]

[REDACTED]

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10.5 Safety analysis

[REDACTED]

All AEs will be coded according to MedDRA.

[REDACTED]

10.6 Handling of missing data

Study data will be presented based on observed cases, i.e. no imputation of missing values will be performed.

10.7 Interim analysis

Not applicable.

10.8 Data monitoring committee

Not applicable.

10.9 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CIP deviations will be listed individually, including subject number and observed deviation.

Deviations from the statistical plan will be documented in the Clinical Study Report.

10.10 Sample size

Sixty subjects were chosen to be enrolled in this study with the aim of fifty subjects completing the study. The sample size has been established based on the probability of detecting an AE given the true population rate of 5%. This 5% criterion has been selected based on this value representing the point-estimate cut-off AE rate for inclusion in product labelling.

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11. Protection of personal data

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the investigation but the data collected until the consent was withdrawn may be used in the statistical analyses.

Authorized representatives from the Sponsor or a RA may visit the investigational site to perform audits/inspections, including source data verification, i.e., comparing data in the subjects' medical records and the eCRF. Data and information will be handled with strict confidentiality.

12. Quality Control and Quality Assurance

12.1 Quality control

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CIP, subsequent amendment(s), GCP and the applicable regulatory requirements.

Any CIP deviation shall be reported in the eCRF, which will be verified, discussed, and collected by the monitor and appropriate actions will be taken. The Investigator is responsible for promptly reporting any deviations from the CIP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the Sponsor as well as the IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP or to terminate the study. Handling of CIP deviations will be performed as described in the monitoring manual.

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12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the Investigator and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on a signature and delegation log.

12.3 Changes to the clinical study protocol

The Investigator and other site personnel involved in the study must not implement any deviation from or changes to the CIP without agreement with the Sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CIP must be documented in a written protocol amendment. However, administrative changes are to be documented in the Sponsor file without requiring a protocol amendment. The Sponsor will assess if the changes require prior FDA approval, and inform the Investigator when such approval has been received.

13. Financing, Indemnification, and Insurance

The CTA outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CIP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/Investigator is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

The Investigator's, Institution's, and Sponsor's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

This study will be displayed on clinicaltrials.gov in accordance with local regulations. The aim is to submit the results of this study for publication. Everyone who is to be listed as an author of the publication shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for

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all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved⁵. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

15. Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IRB or FDA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrollment or non-compliance with the CIP, GCP, or applicable regulatory requirements.

In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

⁵ Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (<http://www.icmje.org>).

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16. References

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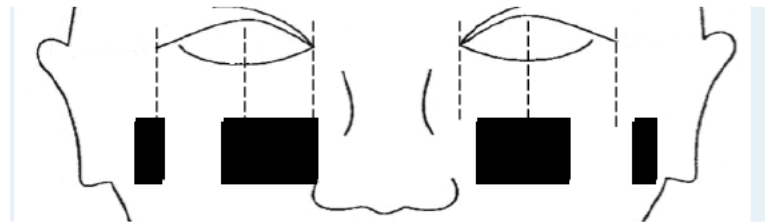
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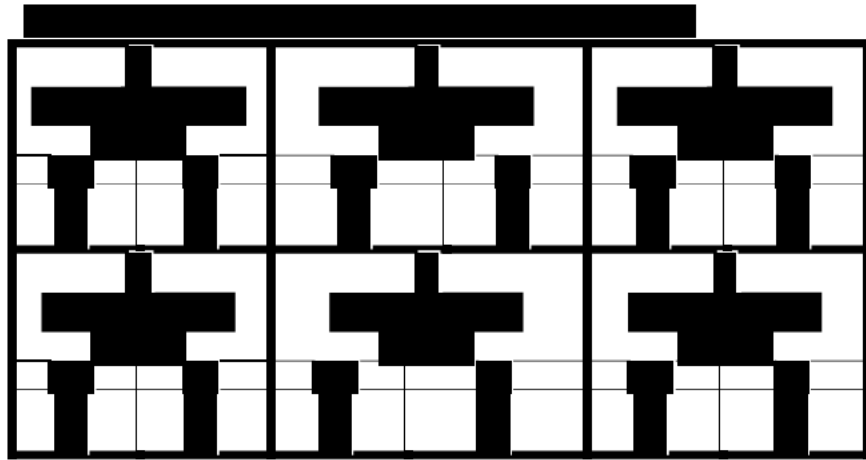
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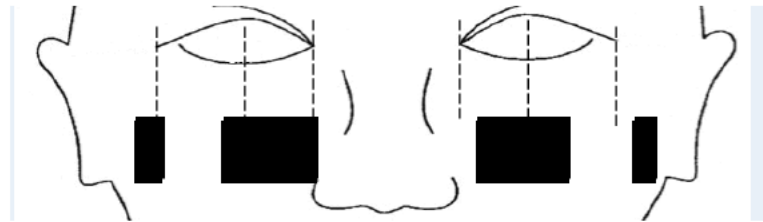
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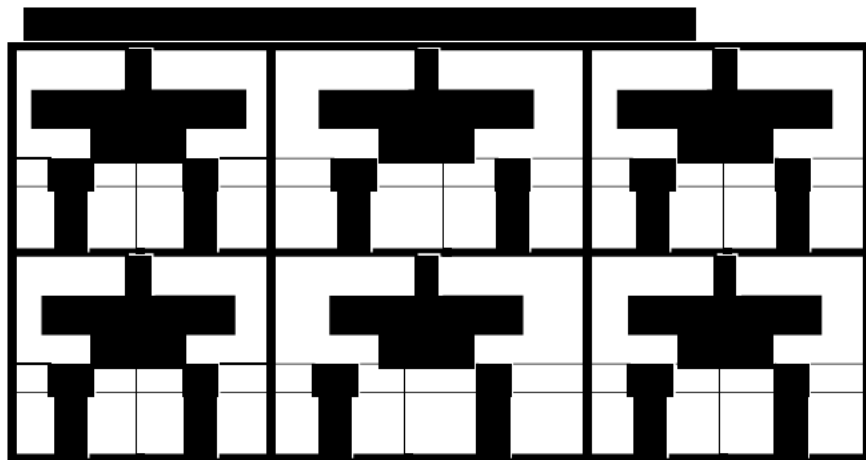
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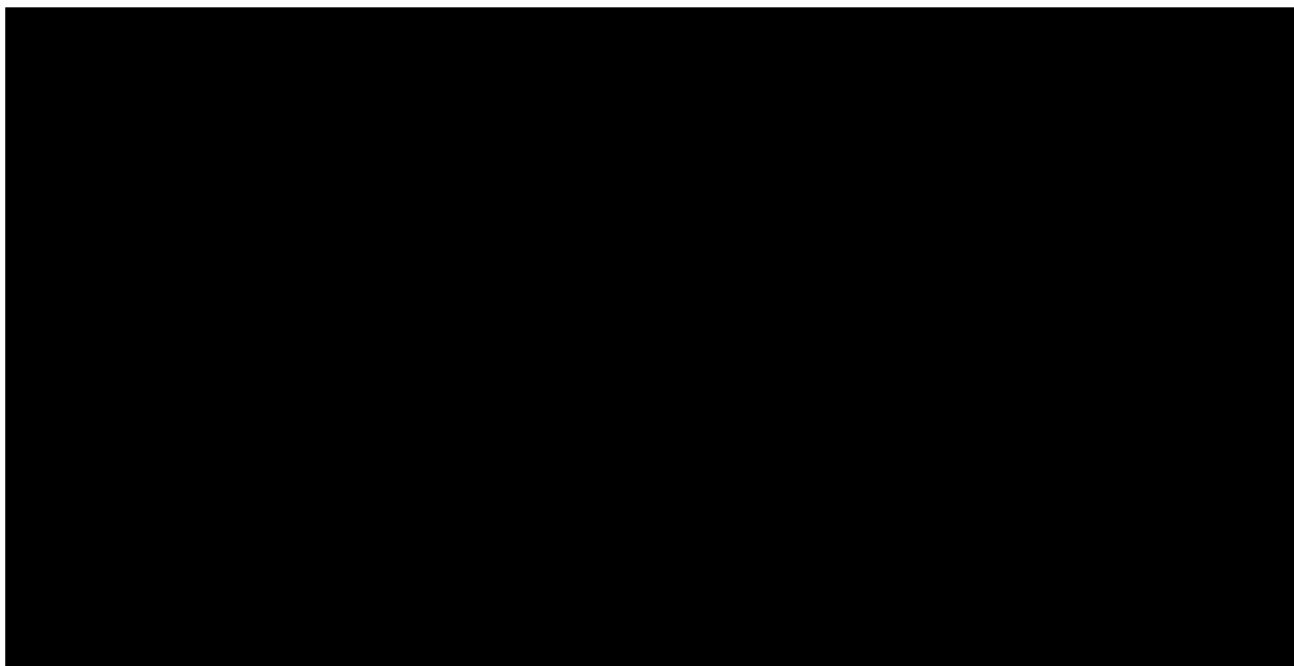
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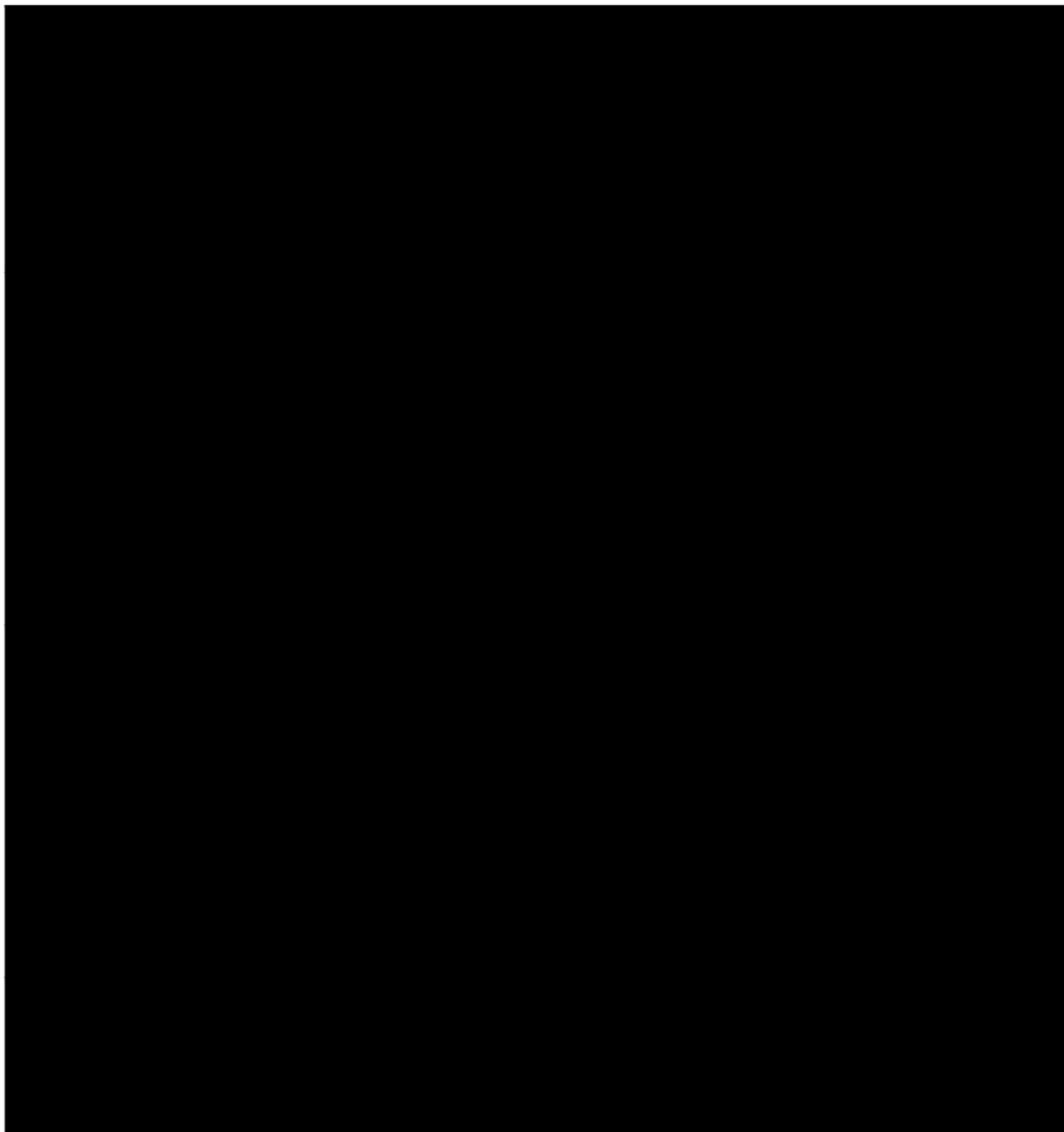


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